Considerations for Development and Marketing of Needleless Naloxone HCl Delivery Systems

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Development Considerations for a Needleless Delivery System

- Indication requirements
- Transmembrane delivery considerations
- Integrating naloxone with a delivery system
- Product performance needs related to safety and efficacy
- Market exclusivity/intellectual property
- Insurance/reimbursement
- Product and development risks
- Capital sources

505(b)(2) New Drug Applications Prescription or OTC

- Old drug in new clothing
- May rely to some degree on FDA's previous findings of safety and efficacy
- Consider the current naloxone injection label indication as a starter

- INDICATIONS AND USAGE
- Naloxone hydrochloride injection is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and certain narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. Naloxone hydrochloride is also indicated for the diagnosis of suspected acute opioid overdosage…

Common Transmembrane Delivery Routes

Routes

- Rectal
- Buccal
- Sublingual
- Intranasal
- Endotracheal
- Pulmonary
- Transdermal

Considerations

- Physiologic environment
- Technical hurdles
- New or old technology
- Patient factors
- Local toxicity
- Product performance
- Variability in performance
- Costs

Desirable New Transmembrane Product Characteristics

- Rapid-acting – functionally equivalent to injection
- Needleless delivery
- Powder or aqueous solution
- Non-toxic to administration site
- Unit-dose and disposable
- Easy to administer
- Acceptable shelf-life
- Durable product design

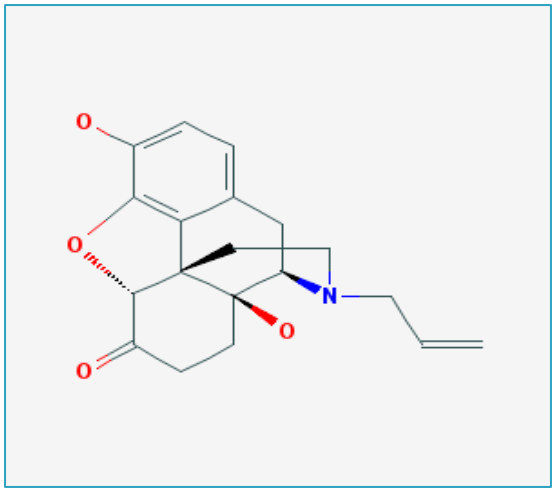
Development Requirements

- Gap analysis of what is known versus what you need to know to meet statutory requirements
- CMC – follow guidance documents for API and the delivery system, i.e., nasal spray, buccal spray, etc.
  - Active Pharmaceutical Ingredient (API) – drug substance
  - Delivery system or device requirements
  - Drug Product requirements
- Toxicology – define systemic exposure and local/regional toxicity to administration site
- Clinical – human exposure profile and proof of safety and efficacy for the indication

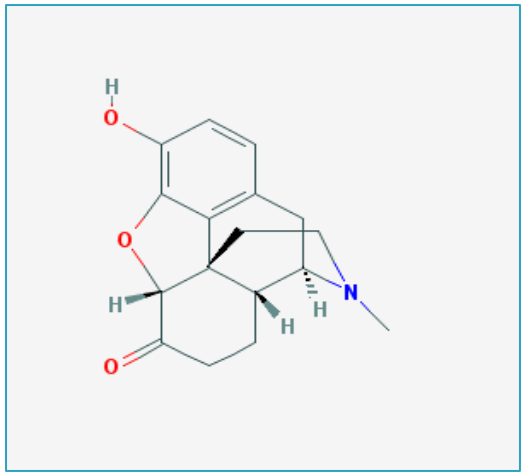
Naloxone HCl Chemistry Consideration for Formulation

Drug Name	Molecular Weight	pKA	Log P – Partition Coefficient
Naloxone HCl	399.87	7.95	1.5
Hydromorp-hone HCl	399.87	8.1	1.3
Naltrexone HCl	377.86	8.13	1.4
Butorphanol tartrate	477.56	~ 8.0	1.8

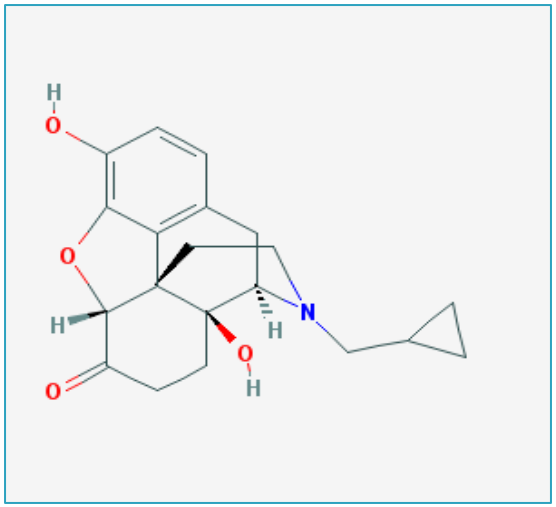
Chemical Structure of Naloxone and Related Molecules



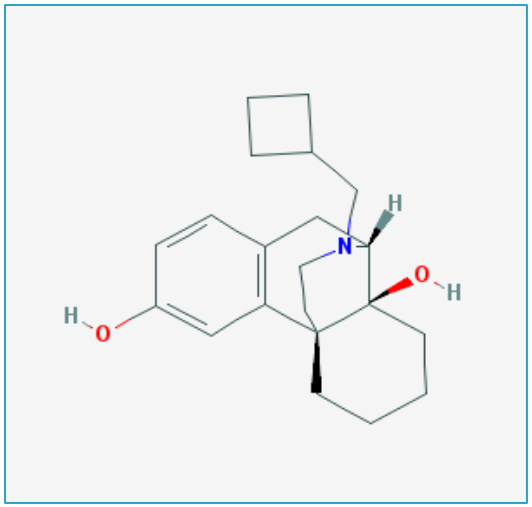
Naloxone



Hydromorphone



Naltrexone



Butorphanol

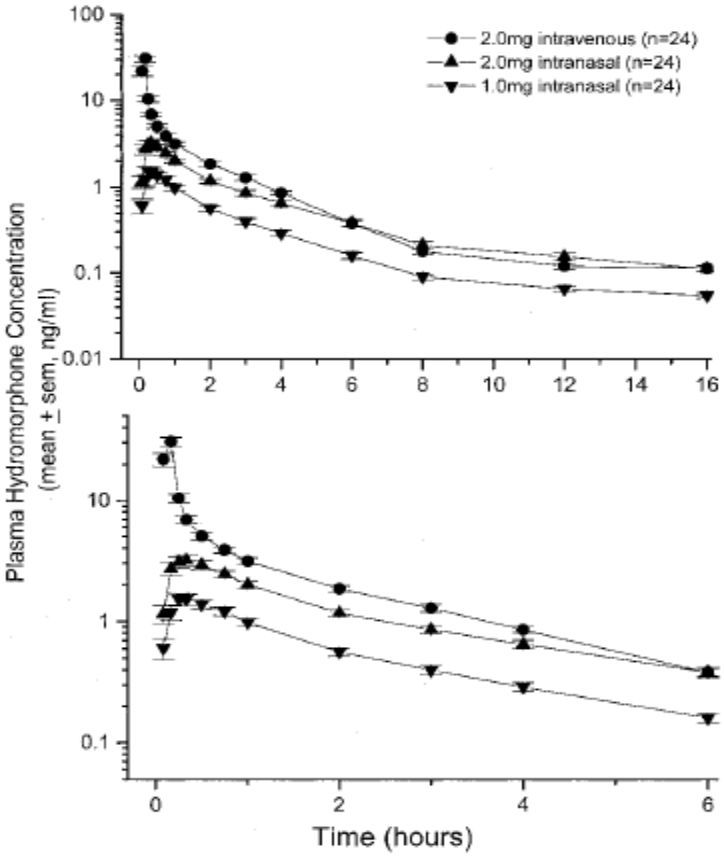
Ref: PubChem 2012

Biopharmaceutics of Intranasal Hydromorphone, Naltrexone and Butorphanol

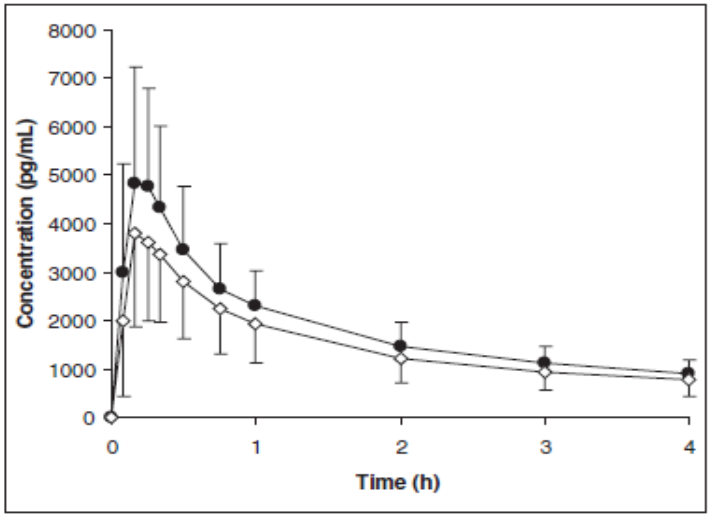
Pharmacokinetic Variable	Bioavailability (%)	Cmax (ng/mL)	Tmax (minutes)
Hydromorphone 2mg	50-60	~ 3.5	20
Naltrexone 10 mg	600 % (Oral)	14.9	22
Butorphanol 2mg	60-70	5.5	10

Ref: Wermeling various

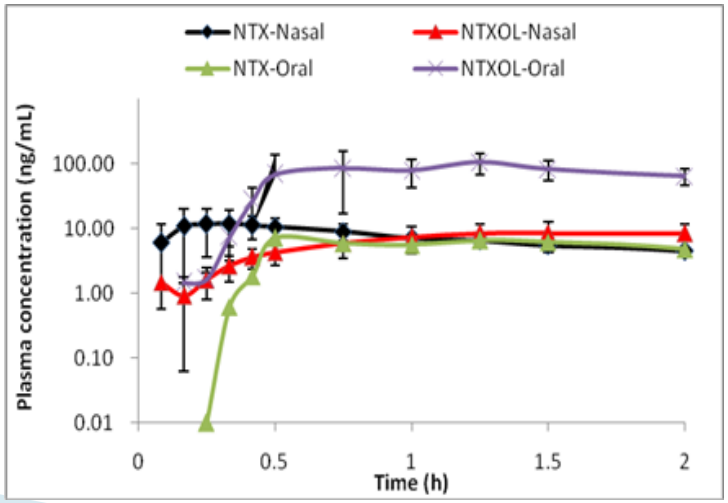
Concentration–Time Profiles after Nasal Administration of Molecules Chemically Related to Naloxone



Hydromorphone 2 mg IV and 1 & 2 mg IN



Butorphanol 1 and 2 mg IN



Naltrexone (NTX) & Metabolite (NTXOL) After 10 mg IN and 50 mg Oral

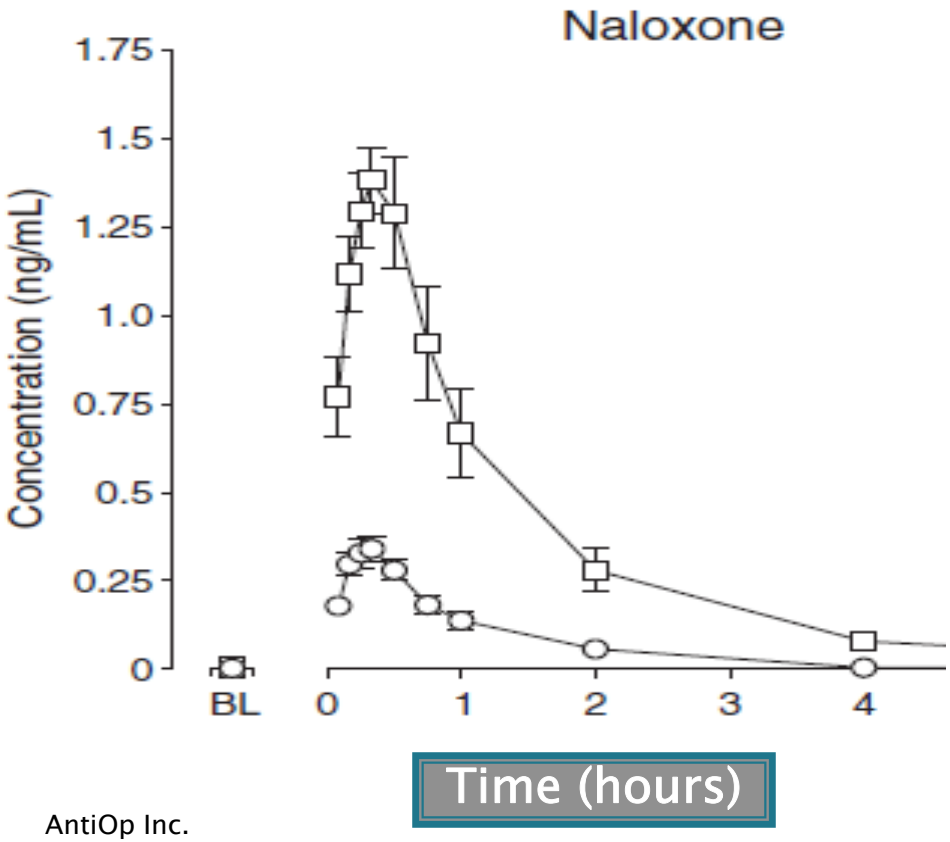
Ref: Wermeling various

Pharmacokinetics of Intranasal Naloxone after Administration of 2mg Powder from Suboxone®

Pharmacokinetic Variables

- Cmax = 1.6 ng/ml
- Tmax = 20 minute
- Bioavailability = 30%

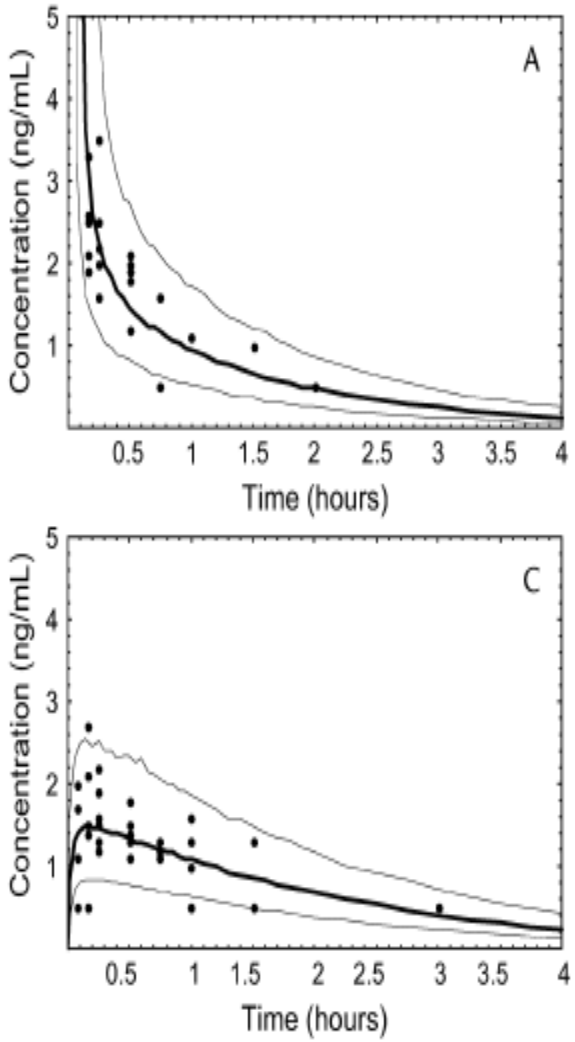
Concentration-Time Profile for 0.5 and 2 mg Naloxone Powder



Ref: Midedleton 2011

Will IN Delivery Result in Comparable Blood Level Exposure?

- Clinically relevant exposure from IN delivery appears to be similar to IM delivery
- Exposure from an optimized nasal formulation is unknown



0.8 mg IV

0.8 mg IM

Ref: Dowling 2006

Treatment of Opioid Overdose with Intranasal Naloxone: San Francisco EMS Protocol

TABLE 1. Intranasal Naloxone Protocol from the Central California EMS Agency

Naloxone
Intranasal (IN)—Administer 2 mg intranasally (1 mg per nostril) using a mucosal atomizer device (MAD) if suspected narcotic intoxication and respiratory depression (rate 8 breaths/min or less) are present. This dose may be repeated in 5 minutes if respiratory depression persists. Respirations should be supported with BVM until the respiratory rate is >8 breaths/min.
Intramuscular (IM)—Administer 1 mg if unable to administer intranasally. May repeat once in 5 minutes.
Intravenous (IV)—Administer 1 mg via slow IV push if there is no response to intranasal or intramuscular administration after 10 minutes.
Pediatric dose—Administer 0.1 mg/kg intranasally, if the patient weighs less than 10 kg and is less than 1 year old.

BVM = bag–valve–mask; EMS = emergency medical services.

Denver EMS Results
2 mg IN vs 1–2 mg IV Naloxone

TABLE 3. Changes in Mean Glasgow Coma Scale Score and Respiratory Rate after Treatment of Positive Responders to Naloxone

	Pretreatment	Posttreatment	p-Value
Intranasal ($n = 33$)			
GCS score	5.2	13.1	0.0001
RR, breaths/min	7.0	16.9	0.0001
Intravenous ($n = 58$)			
GCS score	5.8	12.7	0.0001
RR, breaths/min	9.1	17.8	0.0001

GCS = Glasgow Coma Scale; RR = respiratory rate.

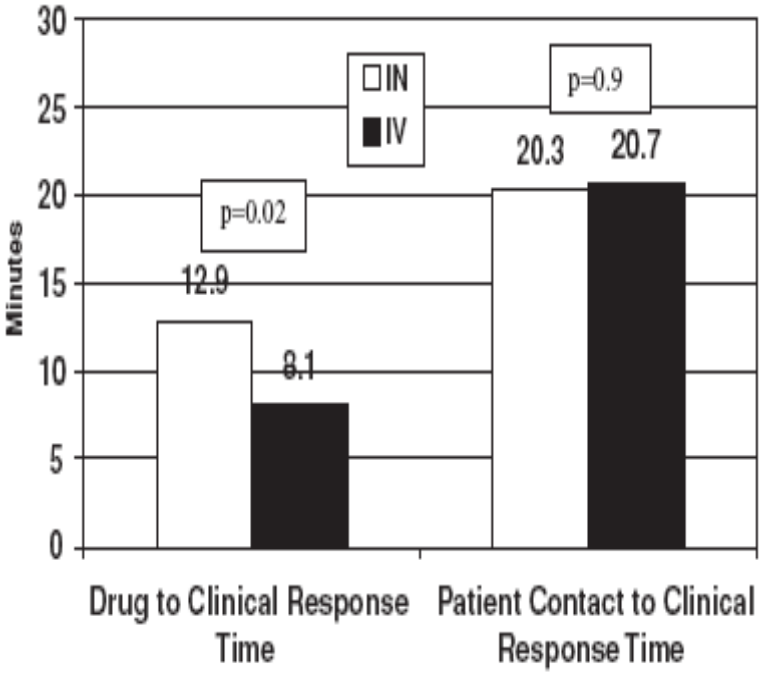


FIGURE 1. Time intervals in minutes. IN = intranasal; IV = intravenous.

Naloxone Drug Delivery Product Market Exclusivity

- Naloxone HCl is off-patent as active ingredient
- Patents on specific delivery platforms may exist
- Nasal delivery patent has expired as prior art
- Specific technology for delivery may provide market protection
  - Special formula method or excipient
  - A device
- Downside is FDA may have not ruled on technology safety and efficacy – more research needed
- 3 years for 505(b)(2), 6 months for pediatrics, and 3 years if OTC
- Not eligible for Orphan Drug designation for this indication

Insurance and Reimbursement

- What is the best mechanism to ensure greatest public access?
  - Medicare, and hence Medicaid and private insurance, will reimburse for Rx with an NDC code
  - **Medicare does not reimburse for OTC drugs**
- If product is OTC then most private insurance will not pay for medication
- It is a legal requirement for pharmacists to offer counseling to patients with a prescription. Not required with OTC.

Private Investment Challenges

- Current entire US naloxone injectable market is $22 M –very small
- Development costs could exceed this amount taking many years of work
- No intellectual property likely unless device/excipient patent
- Limited duration of market exclusivity
- Expanded access market size unknown
- Will prescribers embrace Harm-Reduction principles?
- State laws dictate who can prescribe, dispense and administer medications – Layman Peer to Peer is non-traditional
- Health-care finance uncertainty
  - Rx may get reimbursement from Medicare and insurance
  - OTC drugs not covered by Medicare

Conclusions: Considerations and Risks

- FDA rules for new Rx delivery system of an old drug are described
- Development is contextual – OTC has additional hurdles
- Will there be acceptance of increased price for a specific FDA-approved, ready-to-use, needleless, disposable system?
- Development and marketing feasibility – planning for a needleless naloxone pharmaceutical product must be comprehensive, just as with any other medication – the tests for feasibility are the same as any other medication